Current Emergency and Hospital Medicine Reports (2025) 13:7
https://doi.org/10.1007/s40138-025-00310-4

REVIEW

The Management of Severe Sepsis and Septic Shock: A Novel Update and Bedside Reference Guide

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Accepted: 10 February 2025
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Abstract

Purpose of Review This review highlights recent advances in the treatment of severe sepsis and septic shock, emphasizing new strategies aimed at improving overall survival and reducing mortality in this patient population.

Recent Findings The primary organization responsible for guiding sepsis management is the Surviving Sepsis Campaign (SSC). Several recent studies, which will be summarized in this article, have investigated sepsis screening tools, capillary refill time, antibiotic timing, intravenous fluids, vasopressor use, corticosteroids, and even vitamin C, all of which contribute to the development of new and effective guidelines for managing severe sepsis and septic shock.

Summary Despite years of research on sepsis, ongoing updates continue to introduce new strategies aimed at improving survival rates and reducing mortality. Timely diagnosis, intervention, and disposition are essential for optimizing outcomes. Emergency physicians and intensive care unit specialists will find this thorough review of novel updates in the management of severe sepsis and septic shock particularly valuable. A summary of recommendations which can be utilized as a quick bedside reference is found in Table 1.

Keywords Severe sepsis · Septic shock · Continuing education · Sepsis reference guide · Intravenous fluids · Broad-spectrum antibiotics

Abbreviations

SSC	Surviving sepsis campaign
SIRS	Systemic inflammatory response syndrome
ED	Emergency department
qSOFA	Quick sequential organ failure assessment
NEWS	National early warning score
MEWS	Modified early warning score
CRT	Capillary refill time
CVP	Central venous pressure
ACEP	American college of emergency physicians
IV	Intravenous
CLOVERS	Early restrictive or liberal fluid management for sepsis-induced hypotension
MRSA	Methicillin-resistant staphylococcus aureus
MDR	Multidrug-resistant
MAP	Mean arterial pressure
CENSER	Early use of norepinephrine in septic shock resuscitation
HYPRESS	Hydrocortisone for prevention of septic shock
ALBIOS	Albumin in sepsis
rhAPC	Recombinant human activated protein C
VA-ECMO	Venoarterial extracorporeal membrane oxygenation

Introduction

Sepsis remains a global health challenge, with an estimated 48.9 million cases reported worldwide, approximately 11.0 million sepsis-related deaths between 1990 and 2017, and is now the sixth leading cause of hospitalizations in the United States [1]. In the United States specifically, 1.7 million adults are affected by sepsis annually, with approximately 300,000 deaths. In 2017, it was deemed the most expensive condition treated in US-based hospitals [2]. The high burden of disease underscores the critical importance

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Published online: 08 March 2025

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Table 1 Summary of recommendations and bedside reference guide for the management of severe sepsis and septic shock

Management of Severe Sepsis and Septic Shock Guideline	
Intervention	Recommendation
Screening Tools	Traditional sepsis screening tools like SIRS, NEWS, and MEWS remain more practical for the early detection of sepsis
Lactate Clearance and Capillary Refill Time	No definitive benchmark for guiding resuscitation ni septick shock, though CRT or lactate clearance may be considered
Intravenous Fluids	Administer 30 mL/kg of crystalloid (lactated ringers favored over normal saline) within the first 3 hours of resuscitation. Alternatively, based on CLOVERS trial, early vasopressor use may be considered if the patient is unresponsive to initial crystalloid therapy
Antibiotics	Suspicion of an acute bacterial process, consider a "broad" antimicrobial regimen to be administered within 1 hour of recognizing septic shock, or within 3 hours for sepsis without shock
Vasopressors	30ml/kg crystalloid fluid bolus (SSC guidelines), or consider early vasopressor use, followed by norepinephrine, vasopressin, then epinephrine
Steroids	Administration of corticosteroids in sepsis with vasopressor dependence to improve hemodynamics stability
Vitamin C	Current recommendations advise against the use of intravenous vitamin C
Albumin	Utilize albumin in sepsis patients who have received large volumes of crystalloid fluids or have hypoalbuminemia
Protein C	No current recommendations for the use recombinant human activated protein C
ECMO	Consider VA-ECMO in cases of septic shock with persistent hypotension and cardiac dysfunction that have failed to respond to other resuscitative techniques

of early identification and effective management of sepsis. Since sepsis was first formally defined in 1991, a series of landmark studies and clinical trials have significantly advanced our understanding and treatment of severe sepsis and septic shock.

For instance, in 2001 Rivers et al. demonstrated that early intravenous fluid resuscitation could improve in-hospital survival rates [3], laying the foundation for aggressive early interventions in sepsis care. This study was also instrumental in shaping early goal-directed therapy protocols. Building on this, in 2004, Kumar et al. found that delays in the administration of antibiotics were directly associated with increased mortality, with each hour of delay resulting in a mean reduction in survival by 7.6% [4]. These pivotal studies, among many others, have contributed to the evolving clinical guidelines for sepsis management. However, despite significant advances in this field, mortality rates remain high, indicating further research and improvements in treatment protocols are still necessary.

The formal definition of sepsis refers to a complex pathophysiological process in which a pathogen triggers an initial exaggerated inflammatory-immune response. This heightened response leads to the activation or suppression of multiple biochemical pathways, ultimately resulting in circulatory and metabolic dysfunction [5]. Clinically, sepsis is typically defined as the presence of infection along with at least two of the four systemic inflammatory response syndrome (SIRS) criteria. When sepsis leads to organ dysfunction, it is classified as severe sepsis. A result of this continued dysregulated response is hemodynamic instability despite resuscitation, ultimately classified as "septic shock" [6], characterized by severe circulatory collapse and impaired tissue oxygenation. Septic shock remains one of the leading causes of mortality worldwide.

This article aims to offer a thorough overview of the latest developments in sepsis research, highlighting recent advances in treatment strategies and diagnostic approaches. Each section includes key takeaways designed to provide healthcare providers with practical insights they can apply immediately at the bedside.

Screening Tools

Several screening tools have been developed and tested in the emergency department (ED) to aid in the early identification of sepsis, including the quick Sequential Organ Failure Assessment (qSOFA), the SIRS criteria, the National Early Warning Score (NEWS), and the Modified Early Warning Score (MEWS). Among these, the Sepsis-3 definition introduced qSOFA as the preferred screening tool for early sepsis detection [7]. However, the use of qSOFA has been debated, with the SSC guidelines for 2021 suggesting against its exclusive use and to utilize SIRS, NEWS, or MEWS [8].

A more recent study compared the effectiveness of the SIRS criteria (which include elevated or decreased body temperature, heart rate above 90 beats per minute, respiratory rate greater than 20 breaths per minute, and abnormal white blood cell counts such as neutrophilia above 12,000/mm³ or below 4,000/mm³) with qSOFA (which includes systolic blood pressure < 100 mmHg, respiratory rate > 22 breaths per minute, and a Glasgow Coma Scale score < 15) in identifying patients at risk for sepsis. Additionally, the study compared these tools to a "Sepsis Prediction Model" that generates a sepsis score based on data from the

electronic health record (EHR), confirmed by subsequent clinical diagnosis of sepsis. While the Sepsis Prediction Model showed potential for early detection, its clinical utility was limited by issues related to timeliness, as it often failed to provide early alerts when compared to SIRS and qSOFA [9]. These findings suggest that traditional scoring tools, such as SIRS and qSOFA, continue to be more practical in the ED.

***In summary**, recent studies indicate that traditional sepsis screening tools like SIRS, NEWS, and MEWS remain more practical for the early detection of sepsis, while the use of qSOFA and Sepsis Prediction Models remains a subject of ongoing debate.*

Lactate Clearance and Capillary Refill time (CRT)

Most healthcare institutions are increasingly adopting HER-generated order sets for managing sepsis when it is suspected by practitioners, streamlining the process of initiating timely and appropriate interventions. However, the specific labs required to be ordered as part of this process can vary significantly across different teaching hospitals and healthcare systems. One area of considerable debate has been the role of lactate measurement in the management of sepsis, particularly in relation to lactate clearance. The SSC guidelines for 2021 issued a weak recommendation for measuring blood lactate in sepsis patients, suggesting that if lactate levels are elevated (defined as ≥ 4 mmol/L), clinicians should aim to guide resuscitation efforts by observing a reduction in its value over time [8].

Despite this, the clinical value of lactate clearance remains controversial. The ANDROMEDA-SHOCK trial sought to compare two different resuscitation strategies—one targeting a central venous pressure (CVP) and the other targeting lactate clearance—as a means to reduce 28-day mortality in patients with septic shock. The results showed that the group receiving resuscitation based on CVP (CRT group) had a mortality rate of 34.9%, compared to 43.4% in the lactate-based group [10]. While these results seemed to support the idea that targeting CRT might offer a slight advantage, the findings raised questions about the practical utility of lactate clearance as a goal in guiding fluid resuscitation. One key concern was the potential for over-resuscitation, especially in patients who might already be at risk for volume overload, and whether recognizing and managing volume overload early was more critical to preventing complications than focusing solely on lactate clearance.

The American College of Emergency Physicians (ACEP) also issued a clinical policy stating that serum lactate levels should not be used to guide ongoing intravenous (IV) fluid resuscitation in sepsis. This recommendation is based on the lack of evidence supporting lactate clearance as an accurate marker of a patient's ongoing fluid needs [11].

***In summary**, there is no definitive benchmark for guiding resuscitation in septic shock, though CRT or lactate clearance may be considered as potential approaches.*

Intravenous Fluids

An ongoing debate in sepsis management revolves around intravenous fluid management during the acute phase of septic shock. According to the SSC guidelines, at least 30 mL/kg of intravenous crystalloid should be administered within the first three hours of resuscitation for patients in septic shock or showing signs of hypoperfusion, though this is a weak recommendation [8]. The current preferred fluid is a balanced crystalloid, with lactated Ringer's being favored over normal saline [6], due to the potential for additional acidosis secondary to hyperchloremia. The Early Restrictive or Liberal Fluid Management for Sepsis-Induced Hypotension (CLOVERS) trial compared conventional fluid resuscitation to early vasopressor use and intravenous fluid restriction, finding that the conventional group received about 3.8 L of fluid, while the restriction group received 1.8 L. The trial concluded that after 90 days, mortality and adverse events were similar between the two groups, regardless of the amount of fluid administered [12]. Importantly, the ACEP clinical policy does not recommend a standard fluid bolus but emphasizes the need for individualized fluid resuscitation based on the patient's specific condition [6]. Additionally, the fluid volume guidance provided by the SSC should be adjusted for patients with signs of volume overload or those with known reduced ejection fraction.

***In summary**, the current recommendation is to administer 30 mL/kg of crystalloid (lactated ringers favored over normal saline) within the first 3 h of resuscitation. Alternatively, based on CLOVERS trial, early vasopressor use may be considered if the patient is unresponsive to initial crystalloid therapy, all while using clinical judgment to avoid fluid overload.*

Antibiotics

Empiric broad-spectrum antibiotic therapy has become a cornerstone in the management of severe sepsis and septic shock. The SSC guidelines recommend antimicrobial administration based on factors such as clinical assessment of the likely infectious process, suspicion of methicillin-resistant staphylococcus aureus (MRSA) or multidrug-resistant (MDR) organisms, and potential viral or fungal sources [8]. For example, a negative MRSA nasal swab can eliminate the need for MRSA coverage in septic patients. While no specific antibiotic regimen is universally recommended, broad-spectrum coverage should be initiated within one hour of recognizing septic shock, or within three hours if sepsis is present without shock [6]. Research by Ferrer et al. found

that each hour of delay in antibiotic administration during severe sepsis and septic shock was associated with a significant increase in mortality [13]. Additionally, a retrospective cohort study on door-to-antibiotic time in sepsis patients revealed that a median delay of 166 min resulted in a 19% one-year mortality risk, with each additional hour of delay increasing the odds of mortality by 10% [14].

***In summary**, current recommendations for antibiotic coverage are guided by the suspicion of an acute bacterial process utilizing sepsis screening tools, with a "broad" antimicrobial regimen to be administered within 1 h of recognizing septic shock, or within 3 h for sepsis without shock.*

Vasopressors

The SSC guidelines recommend a step-wise approach to vasopressor therapy following adequate volume resuscitation. First-line therapy is norepinephrine, with vasopressin being weakly recommended as a second option, and epinephrine as a third choice if a mean arterial pressure (MAP) > 65 mmHg cannot be achieved. In cases of cardiac dysfunction, dobutamine may be added to norepinephrine, or epinephrine can be used alone [8]. It is noteworthy that both the Early Use of Norepinephrine in Septic Shock Resuscitation (CENSER) and CLOVERS trials compared standard sepsis management (intravenous fluids followed by vasopressors) with the early use of norepinephrine. The CENSER trial found that early norepinephrine use improved shock control within 6 h compared to standard therapy, while the CLOVERS trial showed no difference in mortality or adverse events between the two approaches [12, 15]. For adults with septic shock on norepinephrine who fail to achieve adequate MAP (< 65 mmHg), the guidelines recommend adding vasopressin rather than increasing norepinephrine doses [6].

***In summary**, vasopressor use in severe sepsis and septic shock follows an algorithm to achieve a MAP > 65 mmHg, starting with a 30ml/kg crystalloid fluid bolus (SSC guidelines) or early vasopressor use based on CLOVERS and CENSER trials, followed by norepinephrine, vasopressin, then epinephrine if there is no underlying cardiac dysfunction suspected (consider dobutamine).*

Steroids

Another area of contention in sepsis management is the use of corticosteroids, particularly in patients requiring vasopressor support. The current recommendation from the SSC supports the use of intravenous corticosteroids in patients who continue to require vasopressor therapy despite adequate fluid resuscitation [8]. This intervention aims to help reduce the duration of vasopressor dependence and improve hemodynamic stability. One commonly used regimen is hydrocortisone, with a typical dose of 200 mg/day, administered either as 50 mg every 6 h or via continuous infusion. This regimen is generally reserved for patients in whom vasopressors remain necessary despite adequate volume resuscitation.

Interestingly, the role of corticosteroids in sepsis management has been challenged by several studies. For example, The Hydrocortisone for Prevention of Septic Shock (HYPRESS) trial, which specifically examined the early use of hydrocortisone in patients with severe sepsis who had not yet developed septic shock, found that hydrocortisone did not significantly reduce the risk of progressing to septic shock within 14 days when compared to a placebo [16]. This trial raised questions about the benefit of early corticosteroid therapy in sepsis, particularly before shock has developed. While corticosteroid use is endorsed by the SSC in patients with persistent shock despite vasopressors, the evidence remains mixed, and clinicians must weigh the risks and benefits on a case-by-case basis.

***In summary**, the SSC recommends the administration of corticosteroids in sepsis with vasopressor dependence to improve hemodynamic stability. **However**, the HYPRESS trial shows no clear benefit in preventing septic shock in non-shocked patients.*

Vitamin C

A study conducted by Lamontagne et al. investigated the effects of intravenous vitamin C in critically ill adults with sepsis who were already receiving vasopressor therapy in the intensive care unit. The study found that patients who were administered vitamin C had a higher risk of death at 28 days compared to those receiving a placebo [17]. This result raised concerns about the potential harmful effects of vitamin C in sepsis management, contradicting earlier hopes that it might have a beneficial role in improving outcomes for septic patients. The findings suggest that, rather than offering therapeutic benefit, vitamin C may increase mortality in this patient population, emphasizing the need for careful consideration when evaluating adjunctive treatments in sepsis care.

***In summary**, current recommendations advise against the use of intravenous vitamin C* [8].

Albumin

The Albumin in Sepsis (ALBIOS) was a large trial that investigated the clinical benefit of albumin replacement therapy in patients with severe sepsis. The study compared the use of albumin in addition to standard crystalloid fluid resuscitation versus crystalloid therapy alone in terms of overall survival of patients. The idea behind this study was the thought that in severe sepsis there is often intravascular

volume depletion and endothelial dysfunction, both of which contribute to tissue hypoperfusion and organ failure. Given albumin's potential role in restoring intravascular volume and its known effects on maintaining oncotic pressure, the ALBIOS study investigated its role in severe sepsis and concluded the addition of albumin did not improve overall survival at 28- and 90-days [18]. Secondary analyses of the study have suggested, however, that there may be a reduced need for renal replacement therapy and a lower incidence of acute kidney injury in the albumin group. The SSC suggests using albumin in sepsis patients who have received large volumes of crystalloid fluids or have hypoalbuminemia [8].

In summary**, **the current recommendation suggests utilizing albumin in sepsis patients who have received large volumes of crystalloid fluids or have hypoalbuminemia [8].

Protein C

The PROWESS-SHOCK trial was deigned to evaluate the efficacy of recombinant human activated protein C (rhAPC) in critically ill patient with septic shock. Specifically, the trial compared rhAPC with placebo to assess its impact on 28-day and 90-day mortality rates. Despite initial hopes that rhAPC might improve outcomes in patients with septic shock, the findings suggested limited or no benefit in terms of survival [19].

In summary**, **there are no current recommendations for the use recombinant human activated protein C in septic shock.

ECMO

A study conducted by Helwani et al. explored the use of venoarterial extracorporeal membrane oxygenation (VA-ECMO) in patients with sepsis-induced cardiomyopathy, highlighting its potential benefit in severe cases of septic shock. The study found that, in patients who exhibit persistent hypotension despite receiving standard interventions for septic shock—such as fluid resuscitation, vasopressors, and inotropes—VA-ECMO may be a valuable therapeutic option [20]. This approach helps to bridge the gap in patients who fail to respond to conventional therapies, offering a potential life-saving intervention in cases where traditional methods fall short. Given the complexity and risk involved in using VA-ECMO, its application should be carefully considered in appropriate clinical settings, particularly when other therapeutic options have been exhausted. The SSC weakly recommends the use of VA-ECMO for persistent hypotension and severe cardiac dysfunction despite the use of other resuscitative strategies [8].

In summary**, **the current recommendation is to utilize VA-ECMO in cases of septic shock with persistent hypotension and cardiac dysfunction that have failed to respond to other resuscitative techniques [8].

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  - This article is explores the role of venoarterial extracorporeal membrane oxygenation (VA-ECMO) as a potential treatment for septic shock, offering new insights into its effectiveness and potential as a life-saving intervention for critically ill patients.

Author Contributions M.C. Wrote the main manuscript. Reviewed and edited the final draft of the manuscript. Assisted with data curation and concept creation.J.G. Reviewed and edited the final draft of the manuscript. Assisted with data curation and concept creation.

Funding This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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